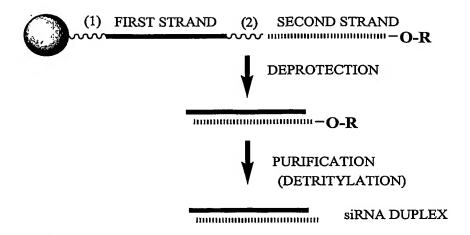
1/25

## Figure 1



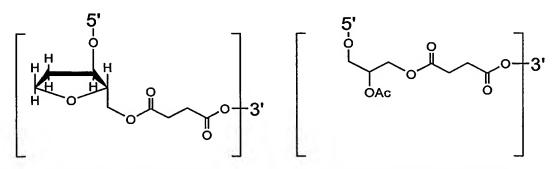
= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

= CLEAVABLE LINKER

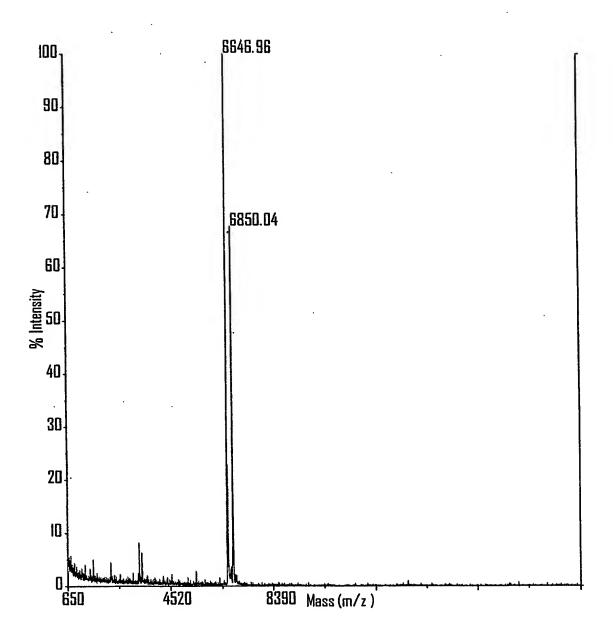
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

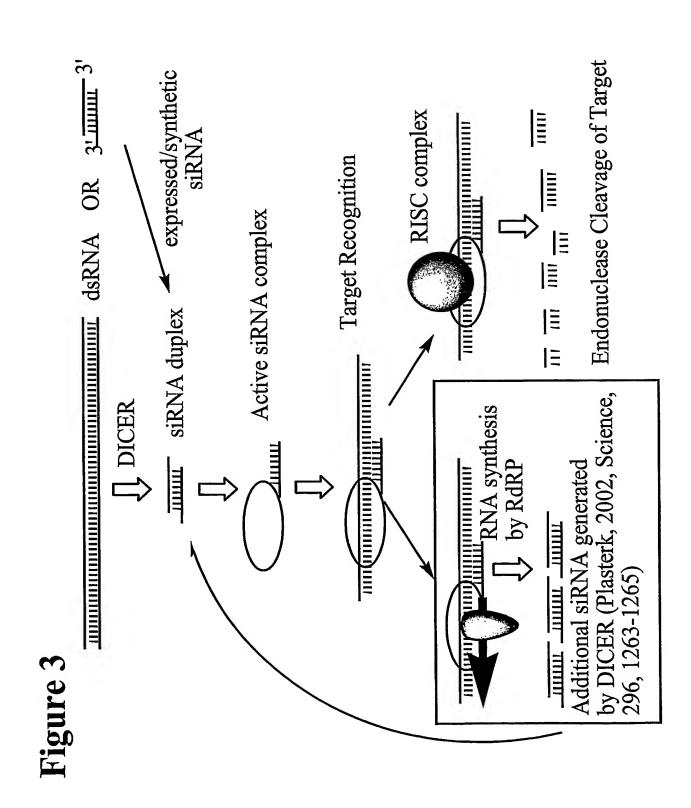


INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Figure 2





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## Figure 4 SENSE STRAND (SEQ ID NO 1039) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N) -3' L-(N<sub>s</sub>N) NNNNNNNNNNNNNNNNNNNN -51 3'-ANTISENSE STRAND (SEQ ID NO 1040) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1041) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N) -3' B -5' 3'-ANTISENSE STRAND (SEQ ID NO 1042) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1043) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N) -3' -5' 3'-ANTISENSE STRAND (SEQ ID NO 1044) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1045) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSÌTIÒNS (N N) AND ALL PURINES = 2'-DEOXY -3' L-(N<sub>5</sub>N) NNNNNNNNNNNNNNNNNNNN -5' 3'-ANTISENSE STRAND (SEQ ID NO 1042) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1046) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) -3' $\mathbf{E}$ L-(N<sub>s</sub>N) NNNNNNNNNNNNNNNNNNNN -5' 3'-ANTISENSE STRAND (SEQ ID NO 1042) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME ÉXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1045) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY -31 5'-B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNN $\mathbf{F}$ -5' 3'-ANTISENSE STRAND (SEQ ID NO 1047) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT

L = GLYCERYL MOIETY THAT IS OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE THAT IS OPTIONALLY ABSENT

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Figure 5 SENSE STRAND (SEQ ID NO 1048) B-GUAUAUAUCAUUGCUGU*TT*-B -3' 3'-L-T<sub>S</sub>TCAUAUAUAUAGUAACGACA -5' ANTISENSE STRAND (SEQ ID NO 1049) SENSE STRAND (SEQ ID NO 1050) 5'--3' guauauaucauugcugu TsT B 3'- $\text{L-}T_{\text{S}}Tc\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,\underline{\mathtt{g}}\,u\,\underline{\mathtt{a}}\,\underline{\mathtt{a}}\,c\,\underline{\mathtt{g}}\,\underline{\mathtt{a}}\,c\,\underline{\mathtt{a}}$ -5' ANTISENSE STRAND (SEQ ID NO 1051) SENSE STRAND (SEQ ID NO 1052) 5'--3' B-GuAuAuAuAucAuuGcuGu TT-B 3'-L-T<sub>S</sub>T c A u A u A u A u A G u A A c G A c A -5' ANTISENSE STRAND (SEQ ID NO 1053) SENSE STRAND (SEQ ID NO 1054) B-GuAuAuAuAucAuuGcuGu TT-B -3' D 3'- $\operatorname{L-}T_{\operatorname{S}}T\,c\,\,\underline{\mathbf{a}}\,u\,\,\underline{\mathbf{a}}\,u\,\,\underline{\mathbf{a}}\,u\,\,\underline{\mathbf{a}}\,u\,\,\underline{\mathbf{a}}\,u\,\,\underline{\mathbf{a}}\,\,\underline{\mathbf{g}}\,u\,\,\underline{\mathbf{a}}\,\underline{\mathbf{a}}\,c\,\,\underline{\mathbf{g}}\,\underline{\mathbf{a}}\,c\,\,\underline{\mathbf{g}}$ -5' ANTISENSE STRAND (SEQ ID NO 1051) SENSE STRAND (SEQ ID NO 1055) 5'--3' B-GuAuAuAuAucAuuGcuGuTT-B  $\mathbf{E}$ 3'- $\operatorname{L-}T_{\operatorname{S}}Tc\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,u\,\underline{\mathtt{a}}\,g\,u\,\underline{\mathtt{a}}\,\underline{\mathtt{a}}\,c\,g\,\underline{\mathtt{a}}\,c\,\underline{\mathtt{a}}$ -5' ANTISENSE STRAND (SEQ ID NO 1051) SENSE STRAND (SEQ ID NO 1054) 5'-B-GuAuAuAuAucAuuGcuGu TT-B -3' F 3'-L-T<sub>S</sub>T c A u A u A u A u A G u A A c G A c A -5' ANTISENSE STRAND (SEQ ID NO 1056)

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

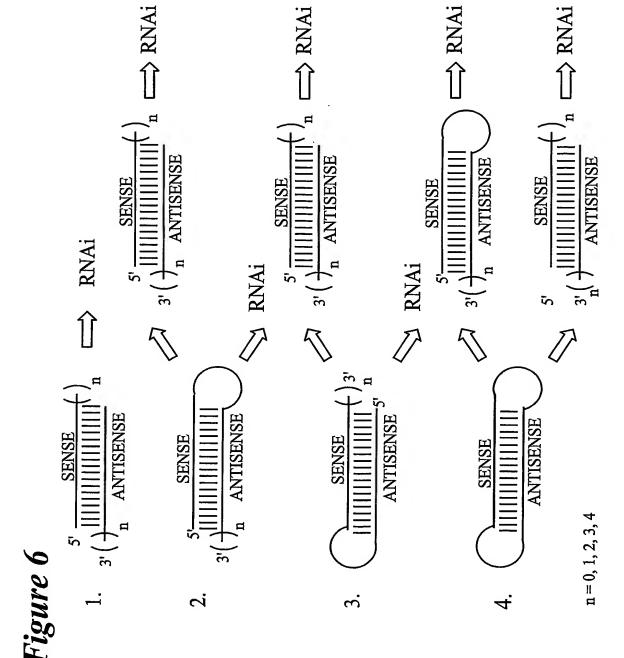
ITALIC UPPER CASE = DEOXY

B = ABASIC, INVERTED ABASIC, INVERTED

NUCLEOTIDE OR OTHER TERMINAL CAP THAT
IS OPTIONALLY PRESENT

L = GLYCERYL MOIETY OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE THAT IS OPTIONALLY
ABSENT



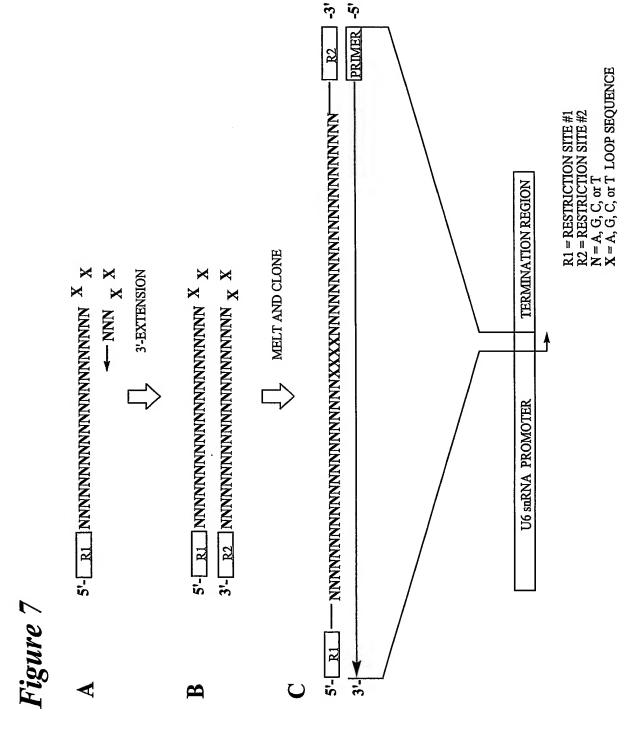


Figure 8

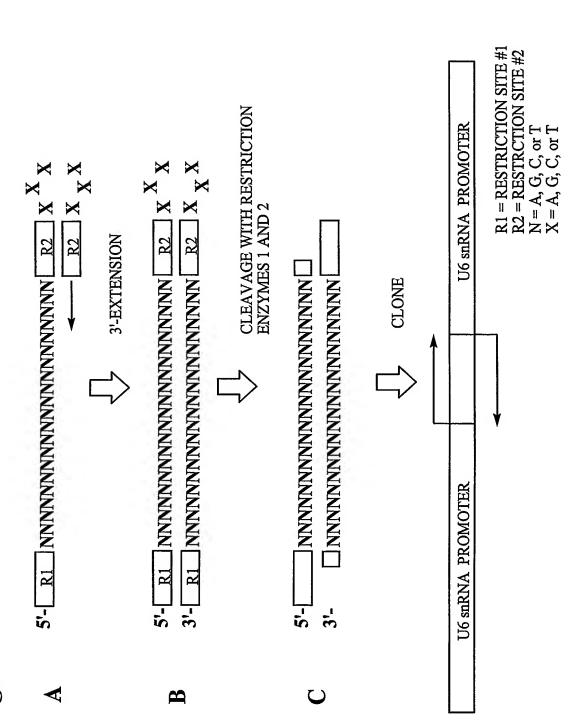
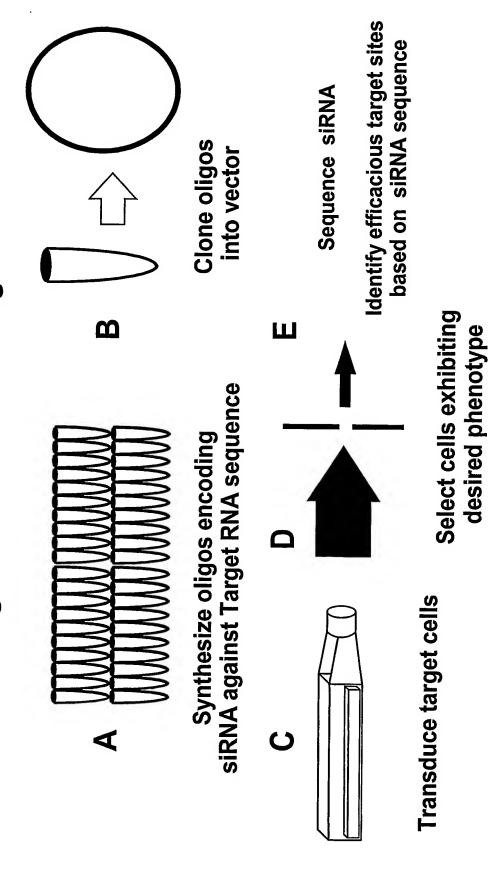
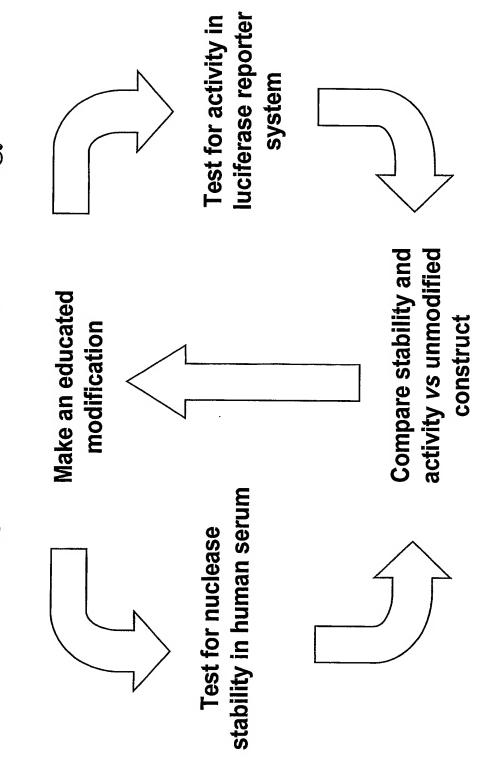


Figure 9: Target site Selection using siRNA

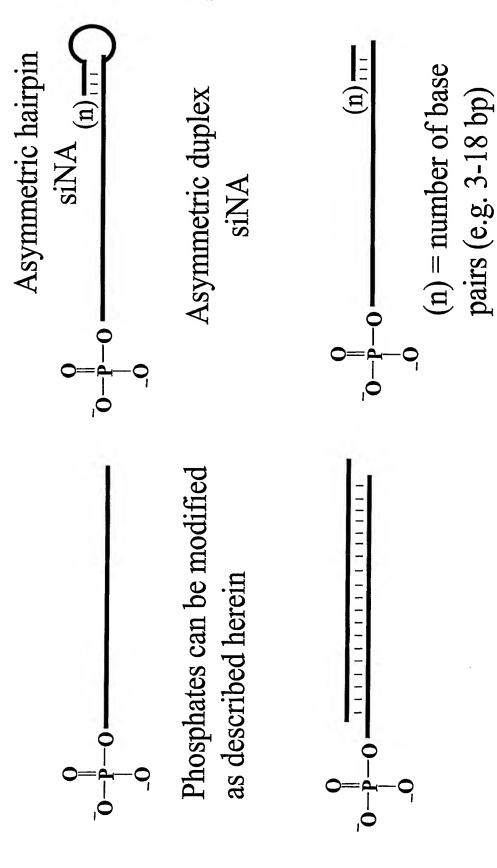


R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

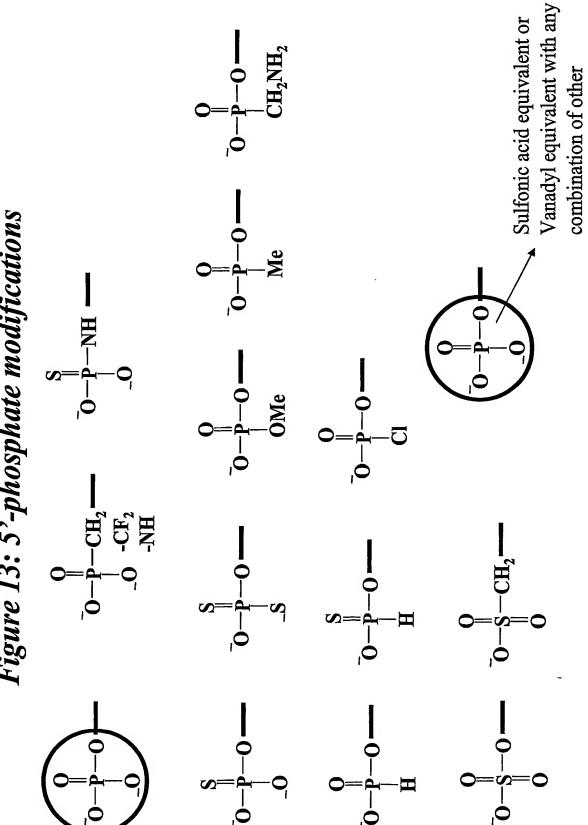
Figure 11: Modification Strategy

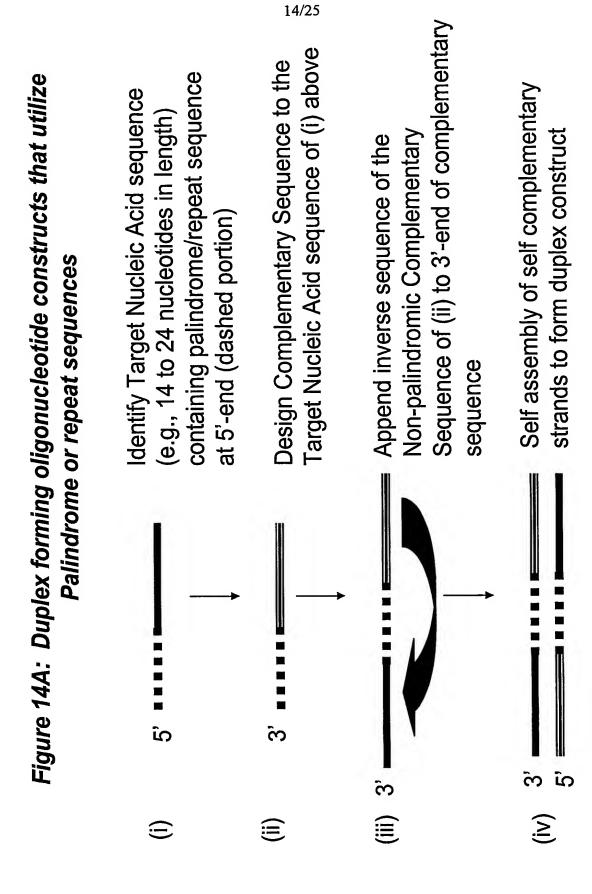


## Figure 12: Phosphorylated siNA constructs



modifications herein





**SEQ ID NO: 1059** 

# Figure 14B: Example of a duplex forming oligonucleotide sequence

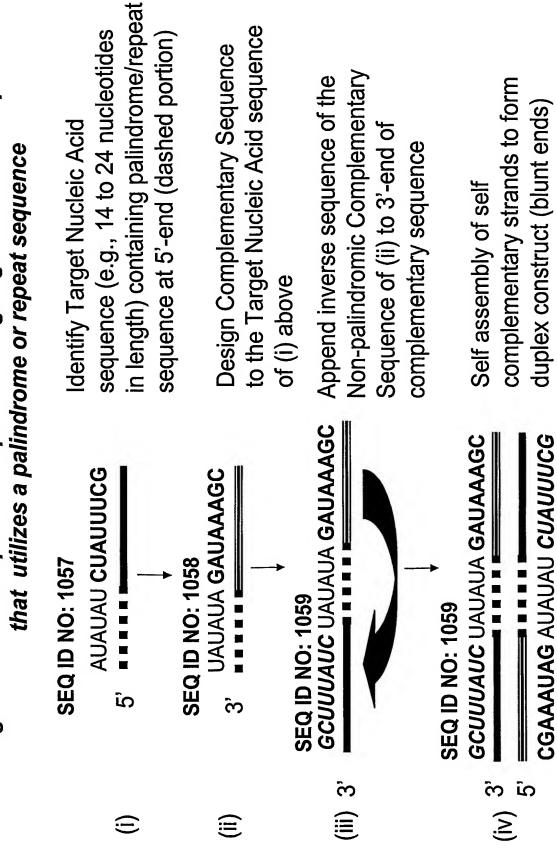


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

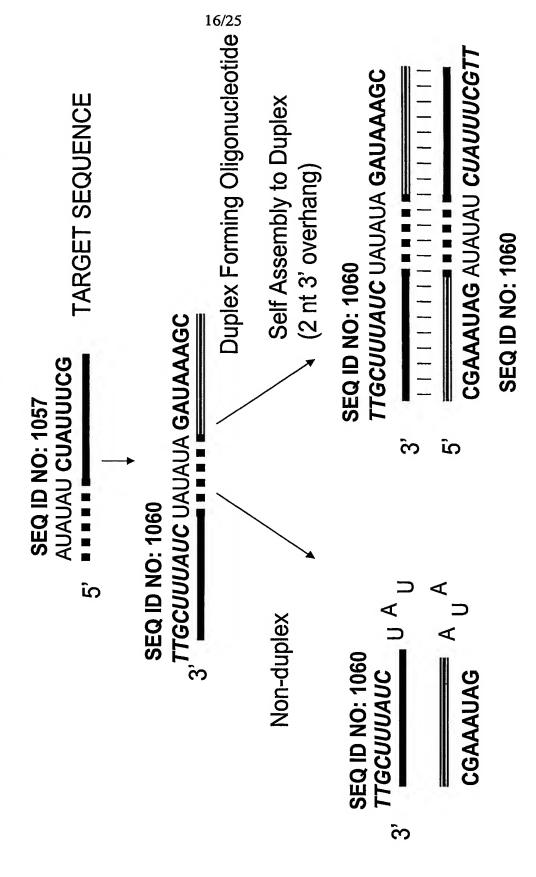


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition

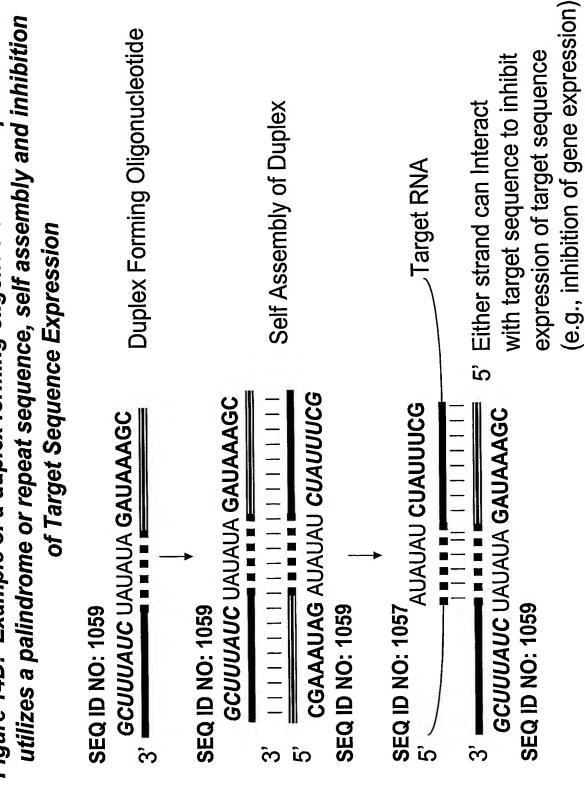
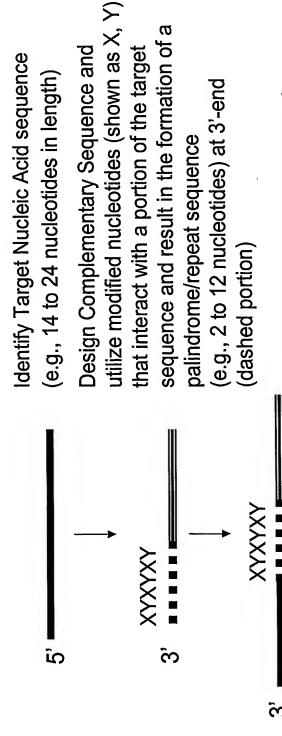
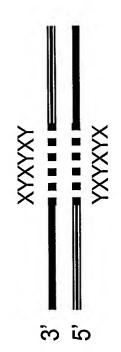


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences



Append inverse sequence of Complementary region to 3'-end of palindrome/repeat sequence

Hybridize self complementary strands to form duplex siNA construct



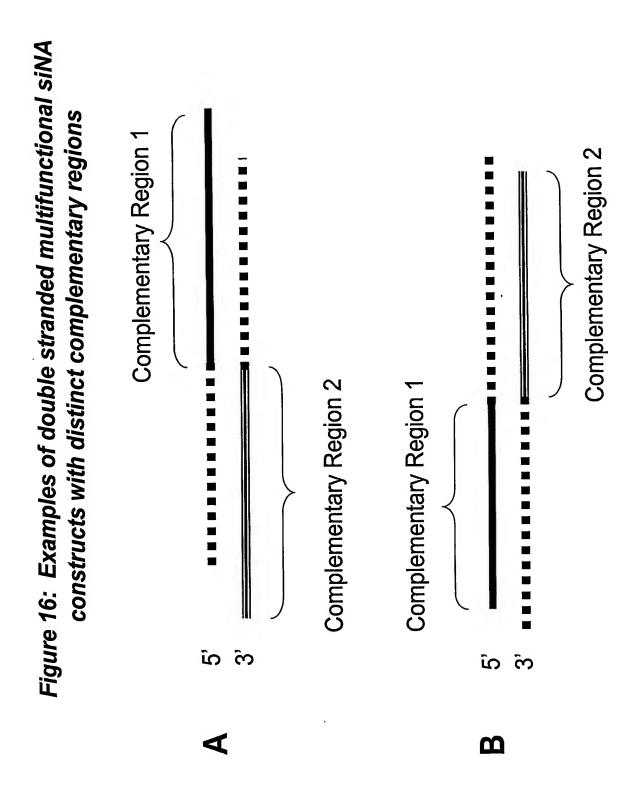
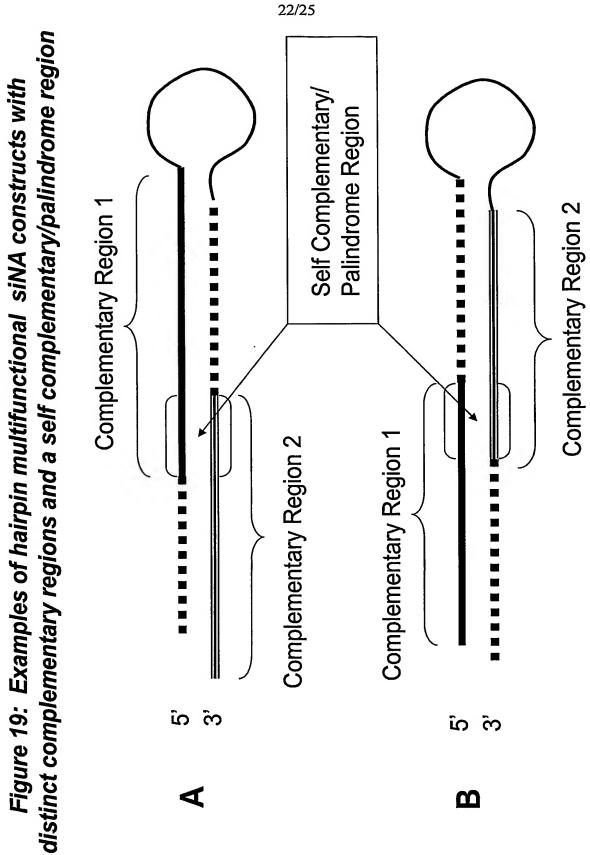


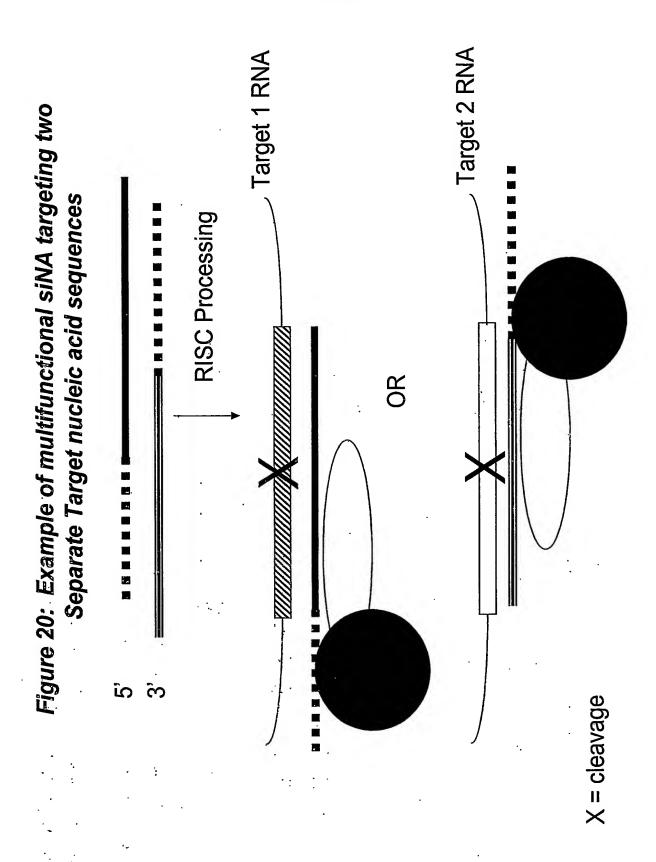
Figure 17: Examples of hairpin multifunctional siNA constructs Complementary Region 2 Complementary Region 1 with distinct complementary regions Complementary Region 1 Complementary Region 2 က် က် က် က်  $\mathbf{\Omega}$ 

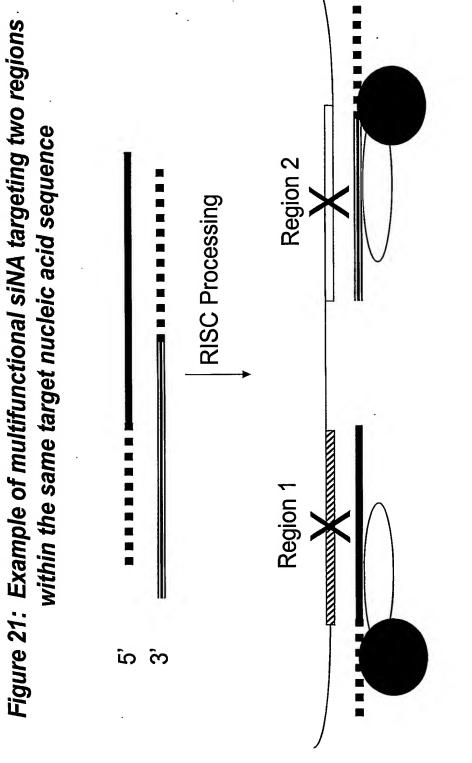
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distinct complementary regions and a self complementary/palindrome region Figure 18: Examples of double stranded multifunctional siNA constructs with Self Complementary/ Palindrome Region Complementary Region 2 Complementary Region 1 Complementary Region 1 Complementary Region 2 Û  $\tilde{\boldsymbol{\omega}}$ က် က်  $\mathbf{\Omega}$ 

WO 2005/014811 PCT/US2004/025589

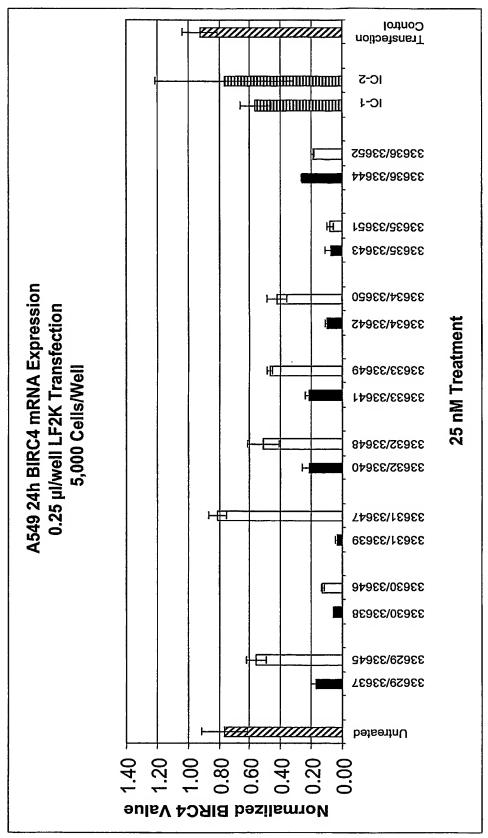






X = cleavage

## FIGURE 22



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